

# **Dry Eye Disease and Computer Simulations - A Literature Review**

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Thesis

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<p>Dry eye disease is one of the most common eye diseases and it deteriorates the life quality of a large number of patients. The etiopathological causes behind the dry eye disease are divided in two major classes, aqueous-deficient dry eye (ADDE) and evaporative dry eye (EDE). Naturally, the reasons behind dry eye symptoms of a certain patient may be a combination of both classes. Knowing the underlying cause behind the symptoms is crucial in finding the correct treatment.</p> <p>Properties of the human tear film have been studied to a great extent. One of the research methods that has been used is computer simulations, especially during the last decades as increases in computing power have made even rather sophisticated models accessible.</p> <p>This literature review first describes the dry eye syndrome as a medical condition and then discusses the pros and cons of computer simulations. Then, key findings from the literature are presented in three categories: macro-scale tear fluid simulations, models of the rupturing process of the thin precorneal tear film, and molecular simulations of the tear film lipid layer. A brief example of a simulation is also presented.</p>			
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1	Introduction .....	1
2	Aims of the study.....	2
3	Theory.....	3
3.1	Tear fluid.....	3
3.2	Dry eye disease .....	4
3.2.1	Aqueous-deficient dry eye.....	5
3.2.2	Evaporative dry eye .....	7
3.3	Computational methods .....	10
4	Materials and methods.....	11
5	Results .....	12
5.1	Fluid flow, composition and deposition .....	12
5.2	Rupturing process of the tear film .....	13
5.3	Molecular simulations of the tear film lipid layer .....	14
5.4	Example of a mass-solute simulation .....	16
6	Discussion.....	19
	References .....	20
	Appendix A .....	23

# 1 Introduction

Tear fluid in human eyes is composed of water and a variety of molecules, such as proteins and lipids. Specific molecular composition and the dynamics of tear fluid secretion and evaporation are related to different types of dry eye disease, with different symptoms and treatment. (1)

Computer simulations are in natural sciences referred to as *in silico* studies. In general, there are two main reasons for using computational methods in medical research. First, it is not always possible, for a variety of reasons, to study a certain phenomenon in laboratory settings, *in vitro*, or on living human or animal test subjects, *in vivo*. Second, computer simulations may offer a new insight that could not even be achieved by other research settings. Many scholars have used *in silico* methods to study the relationship between tear fluid properties and dry eye disease, e.g. (2) and (3).

This study reviews the current body of scientific literature around tear fluid properties in order to find out in which areas such computational methods have been applied. Based on these findings, this study proposes certain key areas where simulations could further our understanding of the dry eye disease.

## 2 Aims of the study

The aim of this study is to provide a summary of the current research literature on computational methods applied to human tear fluid properties.

The research question is formulated as follows: *in which areas, related to human tear film and dry eye syndrome, computational methods have been used and what have been the key contributions of these studies.*

To serve the purpose of this study as a thesis, the scope is narrowed to composition and flow of tear fluid in human eyes, in relation to dry eye disease. Thus, simulations of other related situations, such as tear film and contact lenses, are excluded.

Next chapter explains briefly the current theory behind tear fluid properties and different forms of dry eye syndrome. It also provides a glance to computational methods. Chapter 4 then describes how the literature review was performed. Then, chapter 5 synthesizes the results, and, finally, in chapter 6 the results are discussed more specifically.

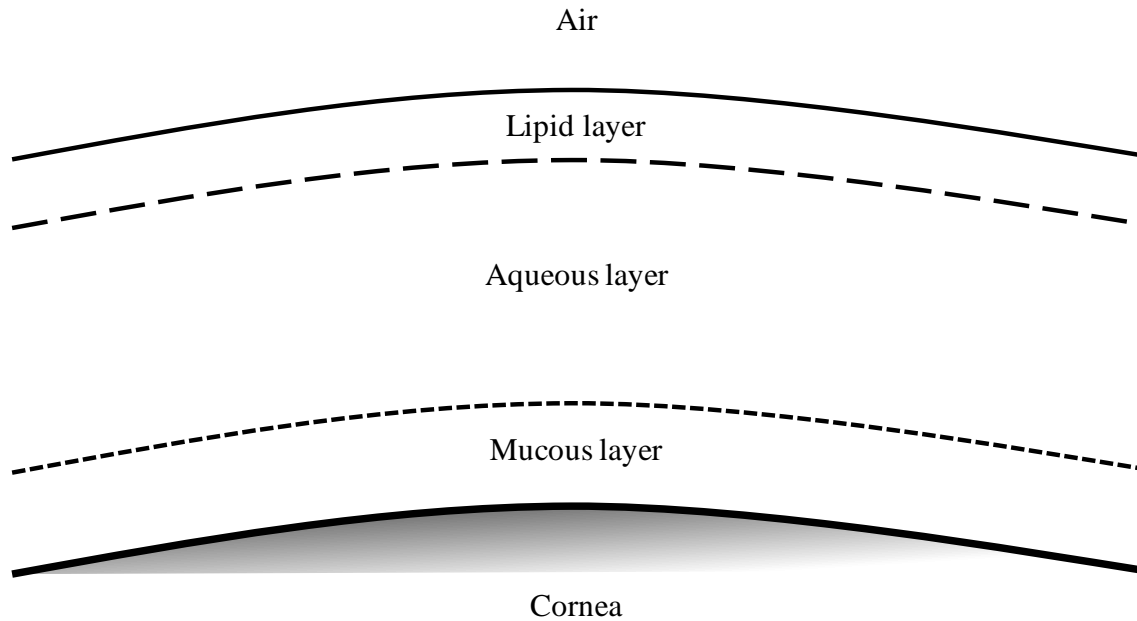
### 3 Theory

This chapter describes the basic theory behind tear fluid in human eyes, dry eye disease as well as computer simulations. The first subchapter is about tear fluid production, composition and flow dynamics. Subchapter 3.2 is to a great extent based on the DEWS report *The Definition and Classification of Dry Eye Disease: Report of the Definition and Classification Subcommittee of the International Dry Eye WorkShop*, which provides a profound synthesis of the current understanding on the dry eye disease. (1) A new version of the report is in progress, expected to be published in 2017, and is not yet available at the moment of writing this thesis. The last subchapter is about computer simulations and why they are useful in studying this subject.

#### 3.1 Tear fluid

The precorneal tear film consists of a trilaminar structure. The three layers are depicted in Figure 1. Lacrimal glands, located in upper lateral sides of the orbits, produce lacrimal fluid which flows medially towards lacrimal puncta. It gathers as lacrimal lakes which are drawn into two puncta. From there tear fluid flows via lacrimal canaliculi into lacrimal sacs, and further via nasolacrimal ducts to nasal cavity. (2) (4)

Next to corneal surface lies the mucous layer, which consists of water, mucins and inorganic salts. Mucins are glycoproteins that have a tendency to bind to water. Mucins are either transmembrane and anchored on underlying cell surfaces with their hydrophobic ends, or secretory, flowing freely within water molecules. Secretory mucins, produced by conjunctival goblet cells, are either soluble or gel-forming, the latter being able to form polymers. (5)



**Figure 1. Tear film consists of three layers: a mucous layer closest to the corneal surface, an aqueous layer, and a lipid layer as the outermost border between eye and air.**

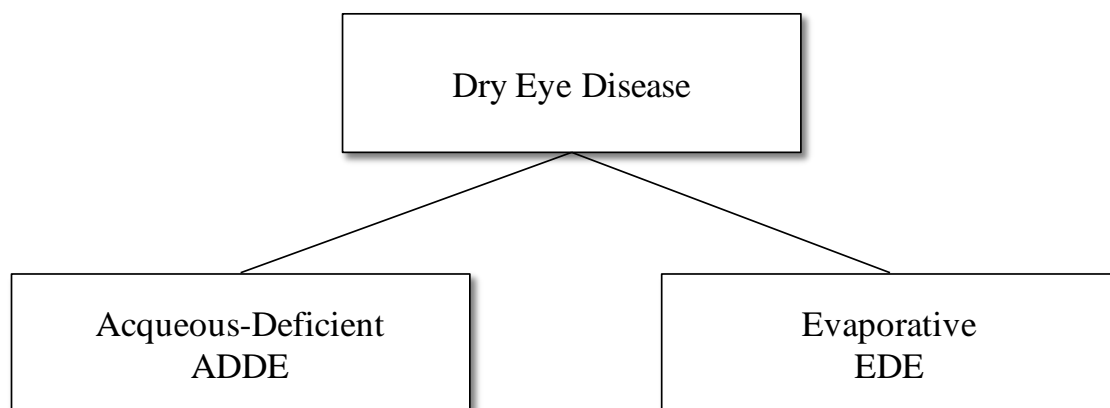
Aqueous tear fluid is secreted from lacrimal glands located in upper temporal sides of the eyes. Tear fluid flows across the eye surface towards nasolacrimal ducts in the nasal corners of the eyes. It consists of not only water but also proteins, electrolytes, anti-microbial factors, cytokines, hormones and immunoglobulins. (5)

Lipid layer is the outermost layer between air and aqueous layer (tear film lipid layer, TFLL). It has a thicker outer nonpolar phase, consisting of wax esters, sterol esters and triglycerides, and a thinner inner polar phase which is mostly formed of phospholipids. One of the most important functions of this layer is thought to be to serve as a barrier for evaporation. It is quite recently discovered that TFLL is a very dynamic structure, flexible as it needs to be able to both squeeze and fold during a blink and also quickly return to its normal state covering the ocular surface during the interblink period. TFLL's efficiency as a barrier to evaporation seems to be more dependent on the composition of the lipids the layer is made of instead of thickness of the layer. (5)

### 3.2 Dry eye disease

The etiopathological causes behind dry eye disease are divided in two major classes, aqueous-deficient dry eye (ADDE) and evaporative dry eye (EDE). Naturally, the reasons behind dry eye symptoms of a certain patient may be a combination of ADDE and EDE.

All causes under both etiologies eventually drive a vicious circle of tear hyperosmolarity and tear film instability. Hyperosmolarity of the tear film stimulates an inflammatory reaction in the ocular surface epithelial cells involving several intracellular pathways. In turn, these changes decrease the stability of the tear film, which, in turn, drives the hyperosmolarity and inflammatory reaction even further. (1)

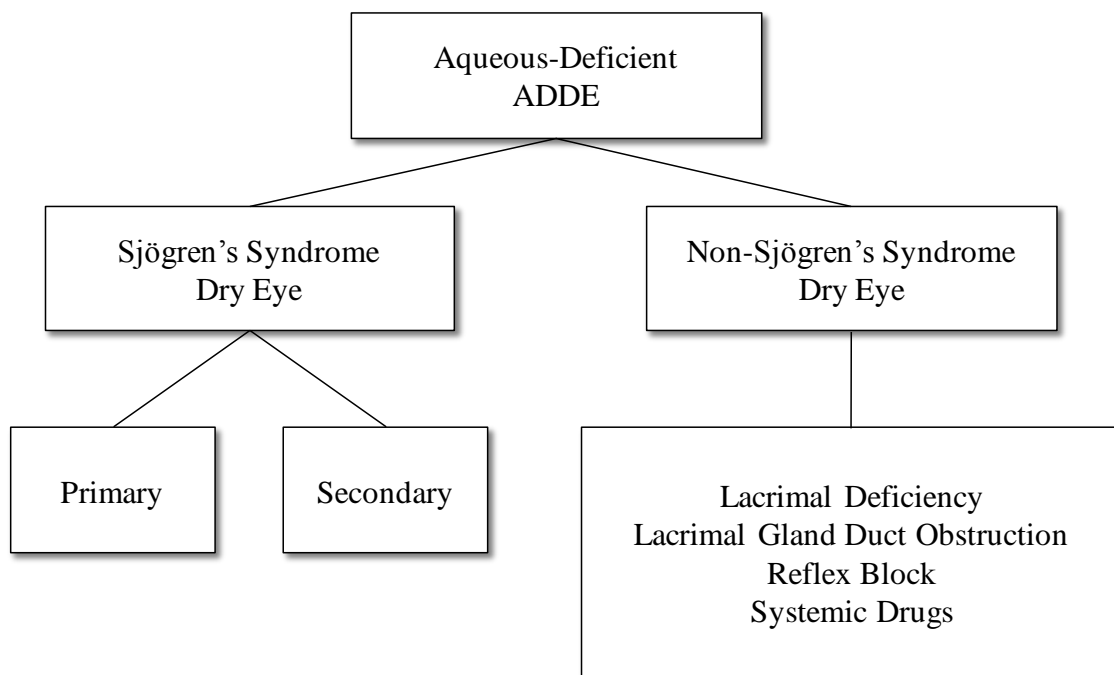


**Figure 2. The two primary classes of dry eye disease are aqueous-deficient and evaporative forms.**

### 3.2.1 Aqueous-deficient dry eye

In the aqueous-deficient form (ADDE), tear secretion is insufficient in order to preserve normal functioning of the tear film. This situation is divided to two subclasses depending on whether the patient is suffering from Sjögren's syndrome or not. (1)





**Figure 3. Aqueous-deficient dry eye disease and its subclasses.**

Sjögren's syndrome, an autoimmune disease, affects external secretory glands in many areas, also in eyes. Activated T-cells attack lacrimal glands in eyes, causing cell death and dysfunction of the glands. Sjögren's syndrome as a cause for dry eyes is divided into primary and secondary form, depending whether there is an overt autoimmune connective tissue disease present or not. (1)

Most commonly ADDE that is not related to Sjögren's syndrome is caused by age (ARDE), although there has been some discussion about how common this phenomenon is. Increasing age may cause lacrimal gland dysfunction due to fibrosis, acinar cell atrophy and periductal blood vessel damage. Also, it has been suggested, that in time, subclinical conjunctivitis might cause excretory duct stenosis. Rarely, lacrimal dysfunction is caused by a gene mutation, as in congenital alacrima or familial dysautonomia. (1)

There is an array of secondary causes for lacrimal gland deficiencies. These causes include infiltrative and/or inflammatory processes such as sarcoidosis, lymphoma, AIDS and graft vs. host disease. Lacrimal gland ablation and lacrimal gland denervation may also cause lowered lacrimal excretion, ultimately leading to dry eyes. In some patients, obstruction of lacrimal gland ducts or lid deformity caused by e.g. chemical or thermal burn, pemphigoid or erythema multiforme is behind dry eyes. (1)

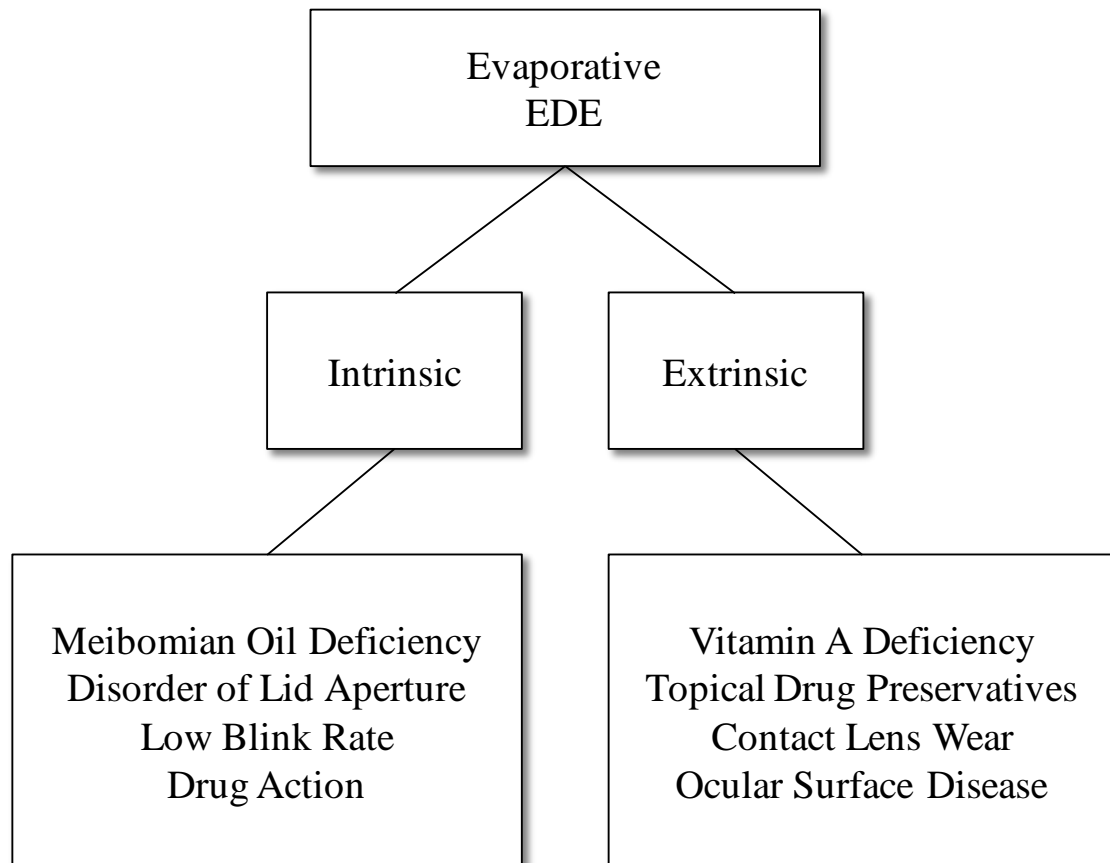
One of the major reasons for ADDE is reflex hyposalivation due to reflex sensory block. Irritation of corneal surface does not lead to proper increase in lacrimal secretion. This might, again, be due to several reasons. The afferent nerve is the ophthalmic branch of trigeminal nerve. It senses stimuli on the corneal surface and drives reflex-induced lacrimal secretion. Reduction of this sensation causes decrease in tear secretion and increase in evaporative loss due to reduced blink rate. One of the most common reasons causing reflex hyposalivation is contact lens wear, where contact lenses reduce corneal sensitivity and thus cause dry eye symptoms via the mechanism described above. This is also the case with some patients who have undergone corneal surgery. Diabetes is a known cause for neuropathy and microvascular changes, and in some studies a correlation between poor glycemic control and dry eye symptoms has been established. The likely reason is reduced reflex tearing. (1)

The efferent end in the reflex-induced lacrimal secretion mechanism is VII cranial nerve. It carries parasympathetic nerve fibers to the lacrimal gland and if this nerve is damaged, tear secretion is reduced. Also, incomplete lid closure may occur and cause increased evaporation. (1)

Certain systemic drugs also share decreased lacrimal secretion as an adverse effect, for example, antihistamines, beta blockers and diuretics. (1)

### 3.2.2 Evaporative dry eye

Etiological causes behind evaporative dry eye disease are divided to intrinsic and extrinsic factors. Both of these classes are discussed in more detail below. In general, all of these reasons increase tear evaporation from the ocular surface, thus predisposing a patient to dry eye symptoms. (1)



**Figure 4. Evaporative dry eye disease and its subclasses.**

Intrinsic factors include meibomian oil deficiency, disorders of lid dynamics, low blink rate and effects of drug action. Extrinsic factors increase evaporation from the ocular surface through vitamin A deficiency, topical drug preservatives, contact lens wear or ocular surface disease such as allergy. (1)

The most common reason for evaporative dry eye is Meibomian gland dysfunction (MGD). Reasons behind the dysfunction vary, the most common reasons being dermatosis such as acne rosacea or atopic dermatitis. Treatment of acne vulgaris with isotretinoin causes a reversible meibomian gland atrophy. In simple MGD the meibomian gland orifices are located in their proper places in the skin of the lid, but in cicatricial MGD the orifices are drawn posteriorly onto the mucosa, which renders delivery of oil to the tear film insufficient. There is a difference in meibomian oil composition regarding cholesterol content between individuals. These differences in the amount of cholesterol, together with differing microbial loads, caused dry eye symptoms. (1)

A rather trivial reason for excess evaporation of water from the tear film is problems with lid dynamics. The aperture may be wider than normally, exposing a larger area of the ocular surface. This may be caused by a physical trauma to the eyelids, a neurological disease, most commonly Parkinson's disease, or simply an upgaze where more ocular surface is exposed to air than in downgaze. Slow blink rate, e.g. while reading or working at a computer, is a known cause for increased evaporation and dry eye symptoms. (1)

Vitamin A deficiency causes dry eye disease through mechanism related to both EDE and ADDE. In the evaporative form, vitamin A is required for goblet cell development and, further, for formation of a functioning glycocalyx. In the aqueous deficient form, vitamin A deficiency may cause lacrimal acinar damage and insufficient tear fluid formation. (1)

Topically applied drugs may cause a toxic reaction on the ocular surface. This is a problem in the group of patients that are required to use topical drugs on a daily basis, e.g. glaucoma patients. Most commonly the reason is in preservatives, e.g. benzalkonium chloride. Also topical anesthetics, especially in chronic use, cause dry eyes. A likely cause is blocking sensory messaging that normally increases blinking and tear production. (1)

Contact lenses are widely adopted in use, and the primary reasons for an individual not to be able to wear contact lenses are discomfort and dryness. The DEWS report describes an incoherency between studies attempting to explain the etiopathological factors causing the symptoms. It seems that the most likely reasons are related to short pre-lens tear film thinning time and, further, changes in tear film lipid composition. Controversies arise from studies on correlation between contact lens water content and dry eye symptoms, where some results showed negative or no correlation. Regarding sex, women seem to be more likely to experience dry eye symptoms while wearing contact lenses than men. It was also possible to predict likelihood to experience dry eye symptoms by using a score on a dry eye questionnaire and measuring non-invasive tear break-up time and meniscus height. (1)

Ocular surface diseases, especially allergic conjunctivitis, are a significant cause of dry eye symptoms. Allergic conjunctivitis is divided to seasonal, vernal keratoconjunctivitis, and atopic keratoconjunctivitis. In the allergic form antigen contact releases inflammatory cytokines from primed mast cells and launches a Th2 mediated response at the ocular surface. As a consequence, goblet cell secretion is increased, membrane mucins are lost

in the aqueous layer, and epithelial cells are lost on both conjunctival and corneal surfaces. Damage to the epithelium pushes the allergic reaction further, resulting in itching, redness, and increased tear production from the lacrimal glands. A chronic situation may lead to ulceration of the surface, which decreases tear film stability and causes local dry spots. Also, Meibomian gland dysfunction changes tear film lipid composition in an unfavorable way, thus strengthening the symptoms of allergic conjunctivitis. (1)

Low androgen and high estrogen levels are associated with dry eyes. This may cause dry eyes e.g. for patients undergoing anti-androgen treatments for prostatic cancer, as well as for women with postmenopausal estrogen therapy. (1)

Lastly, environmental factors may also cause increased evaporation, such as low air humidity or high-speed air flow, resulting in dry eye symptoms. (1)

### 3.3 Computational methods

*In silico* simulation models are used in medical research in areas where it is not possible to study the phenomenon *in vivo* or *in vitro*. Limitations might be related to the very small or large scale of the phenomenon, or e.g. ethical limitations such as in studies using toxic substances (3).

The term *in silico* was coined by Pedro Miramonte, a mathematician from National Autonomous University of Mexico, in his presentation in Los Alamos, New Mexico, in 1989. (6)

Using a mathematical approach usually results in numerical results as well, in addition to the definition of the mathematical model. The purpose of the numerical results is to provide more specific information, often illustrated as charts and figures, as well as to validate the model when the results are compared to prior knowledge on the subject matter.

## 4 Materials and methods

A literature review is a research method where the researcher analyzes previous articles around a certain subject matter. The aim is to provide an answer to a research question using a novel synthesis of the existing literature. A literature review can also serve as a starting point for other studies, such as a new empirical work. (7)

In general, literature reviews can be divided to descriptive and systematic reviews. This study is a descriptive review which follows a less strict methodological process than a systematic review. This approach is suitable for research questions where previous works are scarce and especially if the previous works are not randomized trials or other quantitative studies. (7) (8)

Academic search engines used were Ovid Medline, PubMed and Google Scholar. Keywords included *tear film*, *lipid layer*, *break-up time*, *simulation*, and their different combinations, forms and synonyms, mapped to corresponding search terms. A PubMed search with terms “tear film” and “simulation” provided only 28 results, a rather low number. A closer look at the results revealed that articles refer to *in silico* studies with varying terms, such as simulations, computer models or computational approaches. Thus, searches were performed with different combinations of synonyms and suitable articles were hand-picked from search results based on abstracts.

Reference lists in articles were also used to identify key publications. Results were limited to human tear film properties and dry eye syndrome, excluding studies on other tear film properties or animal studies. Language of the studies was limited to English, and only articles with full text available were used.

## 5 Results

The results fell roughly into three categories:

1. Macro-scale tear fluid simulations focusing on secretion, flow and deposition of fluid in different compartments on the ocular surface
2. Models of the rupturing process of the thin precorneal tear film
3. Molecular level simulations of the tear film lipid layer

The following subchapters summarize findings in each of these categories. A brief mathematical or physical explanation of the underlying models is given for each category.

### 5.1 Fluid flow, composition and deposition

In this category of articles, properties of the tear film are modeled on a macroscopic level. The models focus on flow and dynamics of tear fluid between different compartments of the eye, taking place on a brief time scale after a blink, called the interblink period.

One of the approaches is to use a mass-solute model, which gives the volume and osmolarity of tear fluid in different compartments of the eye. Especially osmolarity has been linked to corneal damage and dry eye syndrome, as was shown in chapter 3. A mass-solute model is a system of differential equations, where the rates of change in volumes and osmolar amounts of solute are sums of fluxes in and out of adjacent compartments.

(2) (9) (10) (11)

In a mass-balance model both fluid and solute are conserved. The rate of change in the amount of fluid or solute in a compartment is the sum of influxes minus all fluxes leaving the compartment. Below is a set of equations based on a model formulated by Gaffney et al. (2) The model consists of three compartments where tear fluid gathers: tear film on the ocular surface (denoted with  $tf$  in the equations below), fornical sacs under the eyelids ( $f$ ), and tear menisci ( $m$ ) that are thicker, curved gatherings of tear fluid next to the borders of upper and lower eyelids.

$$\frac{dV_m}{dt} = q_{from\ tear\ film} - q_{drainage} - q_{evaporation} + q_{from\ fornical\ sac} \quad (1)$$

$$\frac{dV_{tf}}{dt} = q_{evaporation\ from\ tear\ film} - q_{tear\ film\ to\ meniscus} \quad (2)$$

$$\frac{dV_f}{dt} = q_{secretion\ from\ lacrimal\ gland} - q_{fornical\ sac\ to\ meniscus} \quad (3)$$

In the equations above,  $V$  denotes the volume of the tear fluid in each of the compartments in  $m^3$ , and, similarly,  $Q$  denotes the molar quantities of solute in those compartments. Fluxes between compartments, drainage into lacrimal canaliculi and evaporation from compartments are all denoted with  $q$ , in  $m^3/s$ .

The results of these models greatly depend on the variables used, e.g. tear film surface area, evaporation rate, and fluxes between compartments. Those variables are estimates and as such contain a source for error. However, it is possible to test the simulation with different parameter values for e.g. evaporation, which is useful in the case of evaporative dry eye disease. An output from a mass-solute model is demonstrated in chapter 5.4.

This category has advanced scientific knowledge on areas such as effects of evaporation, low secretion and high drainage on the thickness and composition of the tear film, and, for instance, on how long a topical drug remains in tear fluid. Compared to other methods, computer simulations have made it possible to estimate the amounts of tear film in different parts of the eye, which would not be possible with other research methods. Downsides of the research include especially limitations on the physical modeling of the ocular surface (e.g. linear vs. curved surface, simplified flow between strict compartments). Such models are always simplified versions of reality. Another significant downside is that these simulations do not separate different layers of the tear film, but treat them as one uniform layer of liquid. So far it has not been possible to include changes in different layers in these models.

## 5.2 Rupturing process of the tear film

Rupturing of the tear film is a key area regarding the mechanisms of the dry eye syndrome. Tear film ruptures in 15 to 40 seconds for normal individuals, but for people with dry eye disease, break-up time is reduced to as low as a few seconds. (12) This area of simulations utilizes, and partly advances, methods from prior thin film research and lubrication theory.

In these simulations a tear film is modeled as a uniform layer on the ocular surface, swept evenly after an upward movement of the upper lid. Immediately after the blink, the film starts to get thinner due to drainage, evaporation and drainage from the film. Thinning



does not occur evenly, and there are local areas where the process speeds up, and when the film is thin enough, it is ruptured causing increasing discomfort and other symptoms of the dry eye disease. (13) (14) (4)

For an extensive summary on tear film dynamics and lubrication theory, please see Braun's review which presents cases for both single and bilayer models and walks through the formulations behind those models (15). In a Newtonian fluid shear stress is linearly proportional to shear rate. In non-Newtonian fluids this relationship is not a simple linear relation, but increased shear rate causes either increased or decreased viscosity. (16) In a single layer model the tear film is modeled as a Newtonian fluid, only the aqueous layer is taken into account. In bilayer models the underlying mucous layer is treated as another layer with different properties due to the proteins and mucins it contains. (15) A more detailed analysis exceeds the scope of this thesis.

Benefits of this approach come from the possibility to build a model with lid dynamics, evaporation, drainage as well as different fluid properties of tear film, useful e.g. when estimating the effects of viscosity-enhancing eye drops that are widely used in treatment of the symptoms of dry eyes. Treating the tear film as one uniform layer on an even surface is a significant downside. These models do not provide answers to where exactly on the ocular surface and why the thinning starts to occur.

### 5.3 Molecular simulations of the tear film lipid layer

There are several forces through which atoms, or molecules, interact with each other. Strong chemical bonds are covalent bonds that are bonds where atoms share common electrons, ionic bonds resulting from electrostatic attraction between opposite charges, and metallic bonds that arise from conduction electrons surrounding metal ions with positive charges. Weak forces are interactions that are overcome by aforementioned strong bonds. Van der Waals forces are a result of very short, temporary shifts in electron densities; two atoms repel each other at a very short distance of 0,3-0,4 nm, and at a distance of over 6 nm the force becomes practically immeasurable. Dipole-dipole interactions result from permanent positive and negative charges that attract each other. Hydrogen bonds are attractive forces between electronegative oxygen, nitrogen or fluorine atoms that are covalently bonded to hydrogen; high electronegativity causes polarities that attract an opposite charge. A well-known example of hydrogen bonds is between water molecules. (16)

In molecular dynamic simulations locations and velocities of molecules are calculated over a brief time period, typically from nanoseconds to milliseconds. Molecules interact with each other according to the forces described above. An integrator is an algorithm that runs the simulation with discrete time intervals. Molecular simulation settings have different constraints regarding the number of molecules (N), volume (V), temperature (T) and energy (E). In a microcanonical ensemble the number of molecules, volume and energy remain constant (NVE). This may lead to unwanted changes in the stochastic temperature of the system, which, in a canonical ensemble, is controlled by a thermostat (NVT). Occasionally, it is favorable to run a simulation where the pressure remains the same, instead of keeping the volume unchanged. This is achieved with a barostat. (3) (17)

This area is a fine example of the benefits of *in silico* methods, as described in chapter 3.3 above. The exact molecular composition and molecular-level interactions that take place in the lipid layer of the tear film are a natural topic for computer simulations for it is an area that is hard, if not even impossible, to study *in vivo*. This area is closely related to molecular physics and chemistry. *In vivo* and *in vitro* analysis have revealed different types of molecules that the lipid layer contains and these simulations have, in turn, provided valuable insight on how different molecules are deposited in the tear film and how they interact with each other. (18) (19) (20) (21)

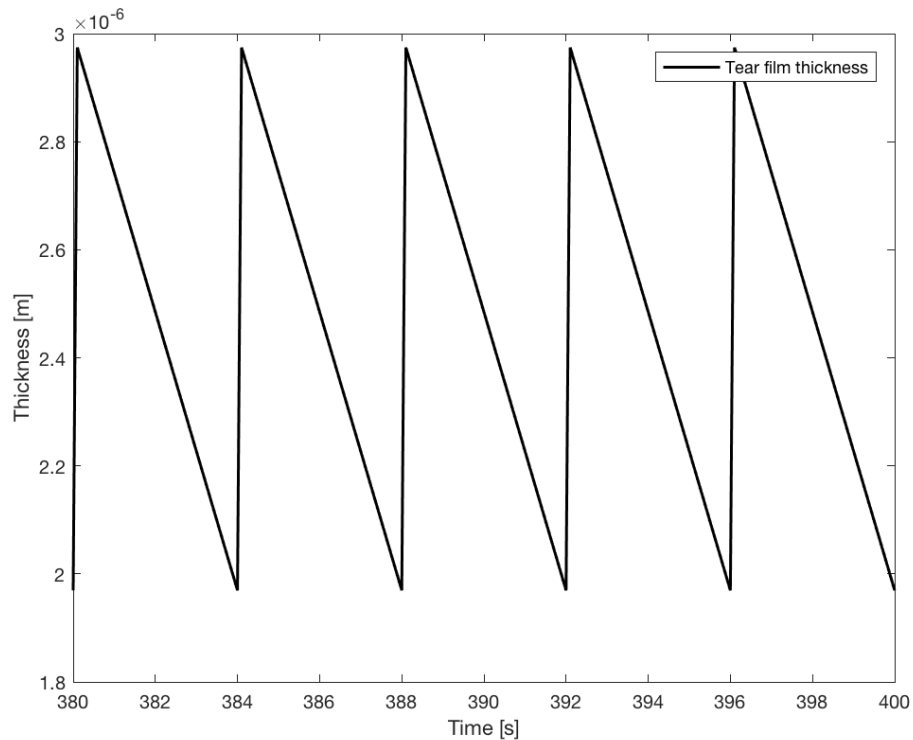
Limitations of these studies are largely caused by available computing power. Simulations take place in very small patches of the tear film, and over a very brief time scale. In theory, it could be possible to model a full tear film on a molecular scale, but such a simulation would require significantly larger computing resources than are available at the moment.

#### 5.4 Example of a mass-solute simulation

Gaffney et al. (2) described a mass-solute model to simulate tear fluid concentrations both in healthy eyes and in patients with dry eye disease. Here the model is reproduced to serve as an example of a computer simulation. Software used was Matlab® version R2016a on an iMac Core i5 3.2 Ghz 5K 27", Late 2015 model.

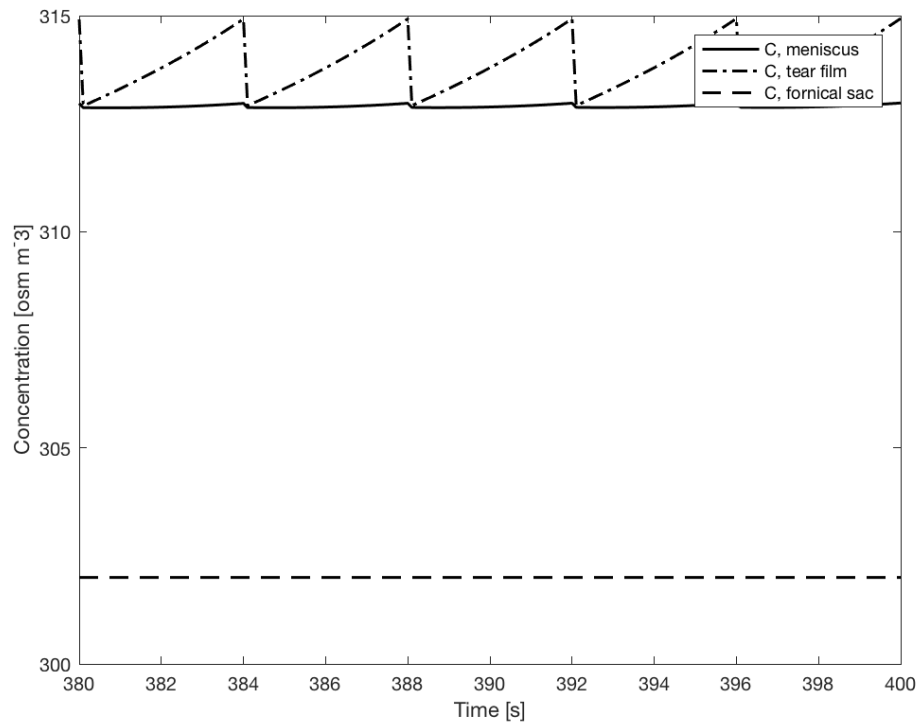
The source code as two Matlab M-scripts is provided in appendix A, released to public domain.

Figure 5 shows how the thickness of the tear film varies between 2 to 3  $\mu\text{m}$  during the interblink period. Various thicknesses have been reported, but King-Smith et al. reported a thickness of 3  $\mu\text{m}$  which is essentially in the same range as this simulation provides (22). The saw-tooth shape is caused by blinking; the time interval between blinks is set to 4 seconds in this example.

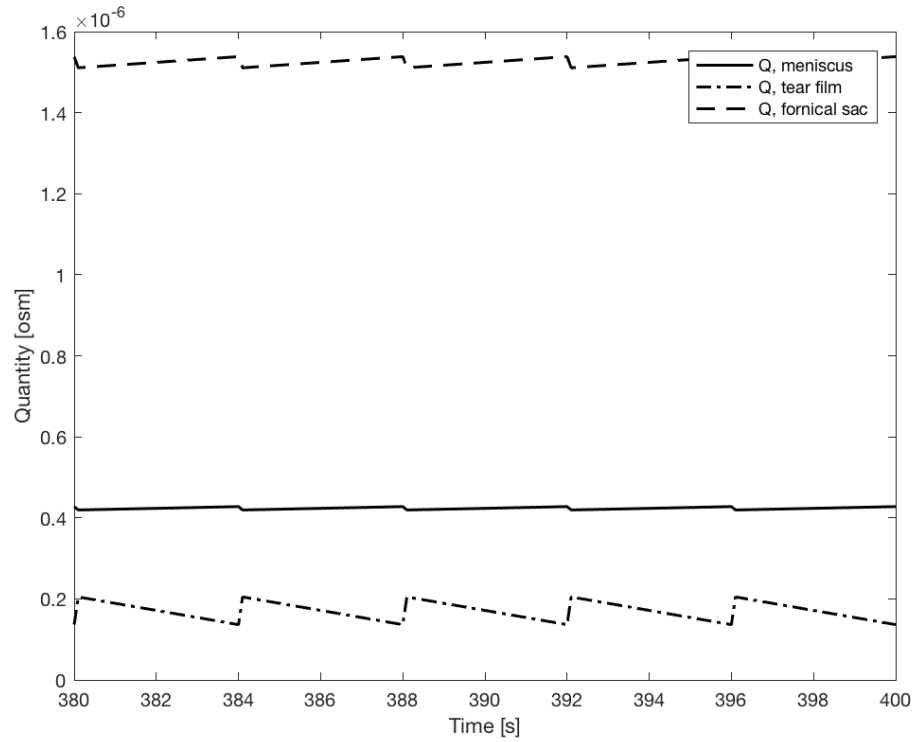


**Figure 5. Tear film thickness in  $\mu\text{m}$ .**

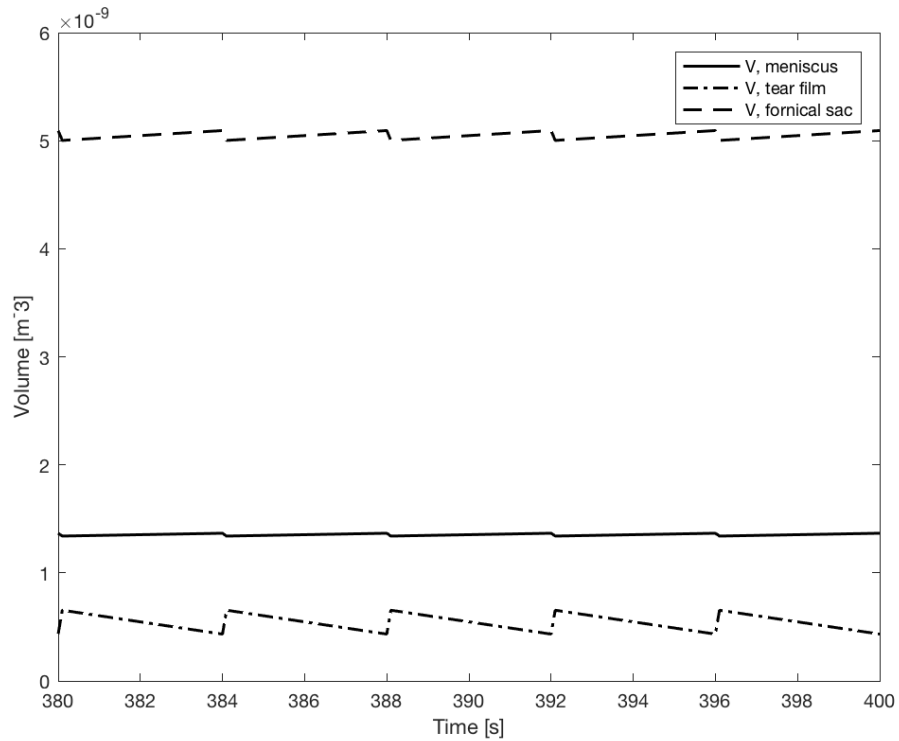
Similarly, Figure 6 presents fluid concentrations in different compartments, calculated from the volumes and molar quantities shown in Figure 7 and in Figure 8. Concentration of tear fluid remains rather stable in fornical sacs, as new fluid with physiological concentration is constantly secreted into them. Largest changes in concentration can be seen in the pre-ocular tear film, in accordance to the observation that increased tear fluid concentration causes discomfort in eyes.



**Figure 6. Concentration of tear fluid in different compartments.**



**Figure 7. Osmolarity of tear fluid in different compartments.**



**Figure 8. Volume of tear fluid in different compartments.**

## 6 Discussion

The aim of this thesis was to perform a literature review in order to find out in which areas, related to human tear film and dry eye syndrome, computational methods have been used and what have been the key contributions of these studies.

As a summary, computational methods (mathematical approaches, numerical simulations) have been used to model tear fluid dynamics, focusing on secretion, flow and deposition of fluid in different compartments on the ocular surface, and further, to estimate e.g. osmolarity of the tear film. Other largely studied area is the thinning and rupturing process of the precorneal tear film. The third area is molecular level simulations of the outermost lipid layer of the tear film. The key contributions, pros and cons of each area, were provided in the previous chapters.

A combination of two or more of these approaches could be a fruitful area for further investigation. The perfect simulation would be a very large scale molecular simulation that spans over the whole ocular surface, spans at least one interblink period and combines i) the effects of different lipid layer compositions on evaporation and tear film folding, spreading and rupturing, ii) flow dynamics as in mass-solute models, and iii) predicts the thinning and rupturing of the tear film. This kind of approach would be sort of a theory of everything when it comes to tear film properties, dry-eye disease and computer simulations. Unrealistic at the moment, but as computers still become more powerful and so-called scalable super computers and cloud or distributed computing services come to a wider use, this might not be a utopist scenario after all. Meanwhile, e.g. bringing other tear film layers and/or ocular surface properties into molecular dynamics simulations in addition to the lipid layer would be interesting. In thinning and rupturing models, including the effects of scratches, veins, molecules and other small structures on the ocular surface would be a significant addition to the models.

## References

1. The definition and classification of dry eye disease: report of the Definition and Classification Subcommittee of the International Dry Eye Workshop. *The Ocular Surface*. 2007; 5(2): p. 75-92.
2. Gaffney E, Tiffany J, Yokoi N, Bron A. A mass and solute balance model for tear volume and osmolarity. *Progress in Retinal and Eye Research*. 2010 January; 29(1): p. 59-78.
3. Telenius J. Properties of the Human Tear Film Lipid Layer. *Insight Through Molecular Simulations*: Aalto University; 2013.
4. Braun RJ, King-Smith PE, Begley CE, Li L, Gewecke NR. Dynamics and function of the tear film in relation to the blink cycle. *Progress in Retinal and Eye Research*. 2015 March; 45: p. 132-164.
5. Johnson ME, Murphy PJ. Changes in the tear film and ocular surface from dry eye syndrome. *Progress in Retinal and Eye Research*. 2004; 23(4): p. 449-474.
6. Wikipedia. In Silico. [Online].; 2016 [cited 2017 4 8]. Available from: [https://en.wikipedia.org/wiki/In\\_silico](https://en.wikipedia.org/wiki/In_silico).
7. Salminen A. Mikä kirjallisuuskatsaus? Vaasan yliopiston julkaisuja. 2011.
8. Kangasniemi M, Utriainen K, Ahonen SM, Pietilä AM, Jääskeläinen P, Liikanen E. Kuvaileva kirjallisuuskatsaus: eteneminen tutkimuskysymyksestä jäsennettyyn tietoon. *Hoitotiede*. 2013; 25(4): p. 291-301.
9. Zhu H, Chauhan A. A Mathematical Model for Ocular Tear and Solute. *Current Eye Research*. 2005; 30(10): p. 841-854.
10. Zhu H, Chauhan A. Tear Dynamics Model. *Current Eye Research*. 2007; 32(3): p. 177-197.

11. Cerretani CF, Radke CJ. Tear Dynamics in Healthy and Dry Eyes. *Current Eye Research*. 2014; 39(6): p. 580-595.
12. Peng CC, Cerretani C, Braun RJ, Radke CJ. Evaporation-driven instability of the precorneal tear film. *Advances in Colloid and Interface Science*. 2014 April; 206: p. 250-264.
13. Braun R, Fitt A. Modelling drainage of the precorneal tear film after a blink. *Mathematical Medicine and Biology*. 2003; 20(1): p. 1-28.
14. Jones MB, Please CP, McElwain DLS, Fulford GR, Roberts AP, Collins MJ. Dynamics of tear film deposition and draining. *Mathematical Medicine and Biology*. 2005 July;(22): p. 265-288.
15. Braun RJ. Dynamics of the Tear Film. *Annual Review of Fluid Mechanics*. 2012; 44: p. 267-297.
16. Halliday D, Resnick R, Walker J. *Principles of Physics*, 10th Edition International Student Version: Wiley; 2014.
17. Wikipedia. Molecular dynamics. [Online].; 2017 [cited 2017 5 28. Available from: [https://en.wikipedia.org/wiki/Molecular\\_dynamics](https://en.wikipedia.org/wiki/Molecular_dynamics).
18. Telenius J, Koivuniemi A, Kulovesi P, Holopainen JM, Vattulainen I. Role of Neutral Lipids in Tear Fluid Lipid Layer: Coarse-Grained Simulation Study. *Langmuir*. 2012; 28(49): p. 17092-17100.
19. Kulovesi P, Telenius J, Koivuniemi A, Brezesinski G, Vattulainen I, Holopainen JM. The impact of lipid composition on the stability of the tear fluid lipid layer. *Soft Matter*. 2012; 8(21): p. 5826-5834.
20. Wizert A, Iskander DR, Cwiklik L. Organization of Lipids in the Tear Film: A Molecular-Level View. *PLOS One*. 2014 March; 9(3).



21. Kulovesi P, Telenius J, Koivuniemi A, Brezesinski G, Rantamäki A, Viitala T, et al. Molecular Organization of the Tear Fluid Lipid Layer. 2010 October; 99(8): p. 2559–2567.
22. King-Smith PE, Fink BA, Fogt N, Nichols KK, Hill RM, Wilson GS. The Thickness of the Human Precorneal Tear Film: Evidence from Reflection Spectra. *Investigative Ophthalmology & Visual Science*. 2000; 41(11): p. 3348-3359.
23. GROMACS. Documentation. [Online].; 2010 [cited 2017 5 27. Available from: <http://www.gromacs.org/Documentation>.

## Appendix A

```
% runtearmodel.m
% Script written by
% Ilkka Hirvonen, University of Helsinki, ilkka.hirvonen@helsinki.fi
% Please notify via email if You use this script in your own work
% Simulation based completely on article Gaffney et al. A mass and solute
% balance model for tear volume and osmolarity in the normal and
% the dry eye. Progress in Retinal and Eye Research 29 (2010) 59-78

% Initial volumes and quantities for isotonic solute with concentration 302 mOsm
ciso = 302;
Vm0 = 1.34e-9;
Vtf0 = 6.6e-10;
Vf0 = 5.0e-9;
Qm0 = ciso*Vm0;
Qt0 = ciso*Vtf0;
Qf0 = ciso*Vf0;
Atf = 2.2e-4;

blink_interval = 4; % seconds
iterations = 100;

[T, Y] = ode45(@tearmodel, [0 blink_interval], [Vm0 Vtf0 Vf0 Qm0 Qt0 Qf0]);

bigT = T;
bigY = Y;

for i = 1:iterations-1;
    % Blinks and mixing, see Gaffney et al. pp 66-67

    Vms = Vm0;
    Vtfs = Vtf0;
    Vfs = Vf0;

    Vme = bigY(end,1);
    Vtfe = bigY(end,2);
    Vfe = bigY(end,3);

    Qme = bigY(end,4);
    Qtfe = bigY(end,5);
    Qfe = bigY(end,6);

    % Minimal mixing
```

```

Qmsmin = Qme - (Vtfs - Vtfe)*Qme/Vme + (Vfe - Vfs)*Qfe/Vfe;
Qtfsmin = Qtfe + (Vtfs - Vtfe)*Qme/Vme;
Qfsmin = Qfe - (Vfe - Vfs)*Qfe/Vfe;

% Maximal mixing

c0max = (Qme + Qtfe + Qfe/Vfe*(Vfe - Vfs))/(Vme + Vtfe + Vfe - Vfs);

Qmsmax = c0max*Vms;
Qtfsmax = c0max*Vtfs;
Qfsmax = Qfe/Vfe*Vfs;

% Intermediate mixing, lambda = 1 for maximal and 0 for minimal mixing

lambda = 1;

Qms = Qme + lambda*(Qmsmax - Qme) + (1-lambda)*(Qmsmin - Qme);
Qtfs = Qtfe + lambda*(Qtfsmax - Qtfe) + (1-lambda)*(Qtfsmin - Qtfe);
Qfs = Qfe + lambda*(Qfsmax - Qfe) + (1-lambda)*(Qfsmin - Qfe);

[T, Y] = ode45(@tearmodel, [0 blink_interval], [VmsVtfsVfsQmsQtfsQfs]);

bigT = [bigT; bigT(end,1) + T(2:end,1)];
bigY = [bigY; Y(2:end,:)];
end

displength = 200;

figure;
plot(bigT(end-displength:end),bigY(end-displength:end,4),'-k',bigT(end-
displength:end),bigY(end-displength:end,5),'-.k',bigT(end-
displength:end),bigY(end-displength:end,6),'--k','LineWidth',1.5);
legend('Q, meniscus','Q, tear film','Q, fornical sac');
xlabel('Time [s]');
ylabel('Quantity [osm]');

figure;
plot(bigT(end-displength:end),bigY(end-displength:end,4)./bigY(end-
displength:end,1),'-k',bigT(end-displength:end),bigY(end-
displength:end,5)./bigY(end-displength:end,2),'-.k',bigT(end-
displength:end),bigY(end-displength:end,6)./bigY(end-displength:end,3),'--
k','LineWidth',1.5);
legend('C, meniscus','C, tear film','C, fornical sac');
xlabel('Time [s]');
ylabel('Concentration [osm m^-3]');

```

```

figure;
plot(bigT(end-displength:end),bigY(end-displength:end,1),'-k',bigT(end-
displength:end),bigY(end-displength:end,2),'-.k',bigT(end-
displength:end),bigY(end-displength:end,3),'--k','LineWidth',1.5);
legend('V, meniscus','V, tear film','V, fornical sac');
xlabel('Time [s]');
ylabel('Volume [m^-3]');

figure;
plot(bigT(end-displength:end),bigY(end-displength:end,2)./Atf,'-
k','LineWidth',1.5);
legend('Tear film thickness');
xlabel('Time [s]');
ylabel('Thickness [m]');

% Tearmodel.m
% Script written by
% Ilkka Hirvonen, University of Helsinki, ilkka.hirvonen@helsinki.fi
% Please notify via email if You use this script in your own work
% Simulation based completely on article Gaffney et al. A mass and solute
% balance model for tear volume and osmolarity in the normal and
% the dry eye. Progress in Retinal and Eye Research 29 (2010) 59-78

function dy = tearmodel(t,y)
dy = zeros(6,1); % dVm, dVtff, dVf, dQm, dQtf, dQf

Jtfm = 5.58e-11;
Jf = 4.7e-12;
Jlg = 2.81e-11;
Jd = 5.37e-11;
Am0 = 2.6e-5;
Atf = 2.2e-4;
er = 4e-9;
clg = 302;

dy(1) = Jtfm - Am0 * er - Jd + Jf; % dVm/dt
dy(2) = -Atf * er - Jtfm;          % dVtff/dt
dy(3) = -Jf + Jlg;                 % dVf/dt

dy(4) = Jtfm*y(5)/y(2) + Jf*y(6)/y(3) - Jd*y(4)/y(1); % dQm/dt
dy(5) = -Jtfm*y(5)/y(2);          % dQtf/dt
dy(6) = -Jf*y(6)/y(3) + Jlg*clg;   % dQf/dt
end

```